Instructions for Use

Pantozol® 40 mg

Active ingredient:
Pantoprazole sodium sesquihydrate

Composition
Active ingredient
1 gastro-resistant tablet contains :
Pantoprazole sodium sesquihydrate 45.1 mg (corresponding to 40 mg pantoprazole)

Pharmacotherapeutic / indication group / action mechanism
Pharmacodynamic properties :
Proton pump inhibitors :
ATC code : A02BC02

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.
Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H^+, K^+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

Pharmacokinetic properties :
- **General pharmacokinetics :**

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 p.a. the maximum serum concentrations of about 2 – 3 µg/ml are achieved, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg. Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific activation of pantoprazole in the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).
Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are virtually linear after both oral and intravenuos administration.
Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5) is not much longer than that of pantoprazole.

- **Bioavailability**

Pantoprazole is completely absorbed after oral administration. The absolute bioavailabil- ity from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

- **Characteristics in patients/special groups of subjects**

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (incl. dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderate delayed half-life (2 – 3 h), excretion is still rapid and thus accumulation does not occur.
Although for patients with liver cirrhosis (classes A and B according to child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5 – 7 fold, the maximum serum concentration only increased slightly by factors of 1.3 -fold in moderate liver impairment subjects and 1.45-fold in severe liver impairment subjects compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Nonclinical Safety Data
Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
In a 2-year carcinogenicity study in rats which corresponds to lifetime treatment for rats – neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic treatment.
In the two-year studies an increased number of liver tumors was observed in rats and female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

Animal Toxicology and/or Pharmacology
A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole – induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects to the thyroid glands are expected.
In animal reproduction studies, signs of fetotoxicity were observed at doses above 3 mg/kg.
Investigations revealed no evidence of impaired fertility or teratogenic effects.

Crossing of the placenta was investigated in the rat and was found to increase with advance gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

Indications
- In combination with two appropriate antibi- otics (see "Posology") for the eradication of *Helicobacter pylori* in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux esophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

Posology and method of administration
- Recommended Dosage:
In *Helicobacter pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *Helicobacter pylori*:

a. 2 x 1 Pantozol 40 mg gastro-resistant tablet / day
   + 2 x 1000 mg amoxycillin / day
   + 2 x 500 mg clarithromycin / day
b. 2 x 1 Pantozol 40 mg gastro-resistant tablet / day
   + 2 x 500 mg metronidazole / day
   + 2 x 500 mg clarithromycin / day
c. 2 x 1 Pantozol 40 mg gastro-resistant tablet / day
   + 2 x 1000 mg amoxycillin / day
   + 2 x 500 mg metronidazole / day

If combination therapy is not an option, e.g. if the patient has tested negative for *Helicobacter pylori*, the following dosage guidelines apply for Pantozol 40 mg monotherapy:

For the treatment of gastric and duodenal ulcer and reflux esophagitis:
One tablet of Pantozol 40 mg gastro-resistant tablet per day.
In individual cases the dose may be doubled (increase to 2 Pantozol 40 mg gastro-resistant tablets daily) especially when there has been no response to other treatment.

For the long-term management of Zollinger- Ellison-Syndrome and other pathological hypersecretory conditions:

Patients should start their treatment with a daily dose of 80 mg (2 tablets of Pantozol 40 mg). Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.
Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

In patients with severe liver impairment, the dose has to be reduced to 1 tablet (40 mg pantoprazole) every other day.
Furthermore, in these patients the liver enzymes should be monitored during Pantoprazole therapy. In the case of a rise of the liver enzymes, Pantoprazole should be discontinued.

The daily dose of 40 mg pantoprazole should not be exceeded in patients with impaired renal function. No dose adjustment is needed in elderly patients. An exception is combination therapy for eradication of Helicobacter pylori, where also elderly patients should receive the usual pantoprazole dose (2 x 40 mg per day) during 1-week treatment.

- General Instructions :
Pantozol 40 mg tablets should not be chewed or crushed, and should be swallowed whole with water 1 hour before breakfast. In combination therapy for eradication of *Helicobacter pylori* infection, the second Pantozol 40 mg tablet should be taken before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged to up to two weeks maximum. If to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dosage recommendations for duodenal and gastric ulcers should be considered.

A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.
A 4-week period is usually required for the treatment of gastric ulcers and reflux esophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Contraindications
Hypersensitivity to the active ingredient(s), or to any of the excipients of the product or the combination product.

Pantozol 40 mg must not be used in combination treatment for eradication of *Helicobacter pylori* in patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of Pantozol 40 mg in combination treatment of these patients.

Special warnings and precautions for use Pantoprazole is not indicated for mild gastrointestinal complaints, such as nervous dyspepsia.
In the case of combination therapy, the summaries of product characteristics of the respective drugs should be observed.

In the presence of alarm symptoms :

Symptomatic response to pantoprazole does not preclude the presence of gastric malignancy.
In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis. Further investigation is to be considered if symptoms persist despite adequate treatment.

Influence on vitamin B12 absorption :
Daily treatment with any acid-suppressing medication over a prolonged period of time (several years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, individuals with reduced body stores or risk factors for reduced vitamin B12 absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Interference with Laboratory Tests:
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, proton pump inhibitor treatment should be stopped 14 days before CgA measurements.

Bone fracture:
PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-doses; defined as multiple daily doses, and long-term PPI therapy (a year or longer).
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Clostridium difficile:
PPI therapy may be associated with an increased risk of Clostridium difficile infection. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Hypomagnesemia:
Has been rarely reported in patients treated with PPIs for at least three months (in most cases after a year of therapy). Serious consequences of hypomagnesemia include tetany, arrhythmia, and seizure. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia *(see Undesirable Effects)*.

In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcaemia and/or hypokalaemia) required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

HIV protease inhibitors:

Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:

Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs (*see Table Undesirable Effects)*. Discontinue pantoprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Subacute Cutaneous Lupus Erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping the product. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Pregnancy and Lactation

Pregnancy

Clinical experience in pregnant women is limited.

Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/ baby.
The potential risk for human is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

Effect on the ability to drive and to use machines
Pantoprazole is not expected to adversely affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

Interaction with Other Medications and Other Forms of Interaction

Drugs with pH-Dependent Absorption Pharmaco- kinetics:

Pantoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of oral bioavailability. (e.g. some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib).

HIV Protease Inhibitors:
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, nelfinavir; due to significant reduction in their bioavailability.

Methotrexate:
Concomitant use with high dose methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Clopidogrel :
Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of pantoprazole.

Other Interaction Studies

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction with other drugs or compounds using the same enzyme system cannot be excluded.

However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids. Human kinetic interaction studies have been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically interactions were found.

Drugs that Inhibit or Induce CYP2C19 (fluvoxamine):
Inhibitors of CYP2C19, such as fluvoxamine, would likely increase the systemic exposure of pantoprazole.

Inducers of CYP2C19 would likely decrease the systemic exposure to pantoprazole.

Incorrect use and overdosage
There are no known symptoms of overdosage in man. In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication apply. If you have taken too little Pantozol 40 mg or have forgotten to take it do not take the dose late, but continue with the next regular dose on your dosing schedule.

Talk to your doctor if you want to interrupt or prematurely discontinue treatment with Pantozol 40 mg.

Storage conditions
Store below 30°C.

Shelf Life :
36 months

Box, 1 blister @ 7 tablets

Reg.No. DKI1553300715B1

On Medical Prescription Only

HARUS DENGAN RESEP DOKTER

Keep out of reach of children!

Imported by:
PT Takeda Indonesia

Manufactured by:
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Production Site Oranienburg
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Table 1 lists adverse drug reactions reported with pantoprazole in clinical studies and postmarketing experience. The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 lists adverse drug reactions reported with pantoprazole in clinical studies and postmarketing experience.

Frequency / System Organ Class	Common (>1/100, <1/10)	Uncommon (>1/1,000,<1/100)	Rare (<1/1,000,>1/10,000)	Very rare (<1/10,000,incl. isolated reports)	NotKnown	
Blood and lymphatic system			Agranulocytosis	Leukopenia; Thrombocytopenia; Pancytopenia		
Gastrointestinal disorders		Nausea/Vomiting; Diarrhoea; constipation; dry mouth; abdominal pain: flatulence; abdominal distension and bloating ; discomfort				
General disorder and administration site conditions		Asthenia; fatique and malaise	Body temperature increased; oedema pheripheral			
Hepatobiliary disorders		Liver enzymes increases (transamines, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)			
Musculoskeletal, connective tissue disorders			Arthralgia ; Myalgia		Fracture of wrist, hip and spine	
Nervous system disorders		Headache; Dizziness	Taste disorder			
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation	Hallucination; confusion	
Renal and urinary disorders					Tubulointerstitial nephritis (TIN) (with possible progression to renal failure)	
Skin and subcutaneous tissue disorders		Allergic reactions such as pruritus ; skin rash/ exanthema/ eruption	Urticaria; Angioedema		Stevens-Johnson Syndrome(SJS); Toxic epidermal Necrolysis(TEN); Drug reaction with eosinophilia and systemic symptoms(DRESS); Acute generalized exanthematous pustulosis(AGEP); Erythema multiforme; Photosensitivity	
Metabolism and Nutrition disorders			Elevated triglycerides weight changes; hyperlipidemias		Hypomagnesemia hyponatremia; Hypocalcemia*; Hypokalemia*	
Eye disorders			Disturbances in visions / blurred vision			
Reproductive			Gynaecomastia			